Interview

Applicants would like to thank Examiner Thai-An N. Ton of the USPTO for the Interview conducted on June 26, 2003. In the Interview, the Examiner agreed that the rejections under 35 USC 112 will be withdrawn if Applicants submit a Declaration showing that although the subject Application includes examples directed to the ability of embryonic stem cells derived from three mice strains to differentiate to dendritic cells in the presence of IL-3 with or without GM-CSF, one skilled in the art is enabled without undue experimentation to make any embryonic stem cells population, namely embryonic stem cells derived from other mouse strains as well as from other mammals including human.

REMARKS

Claims 64, 68-95, 105-108 and 110 are currently pending in the application. The specification was amended to include Applicants' claim for foreign priority, to include an Abstract on a separate page and to include section headings where appropriate.

REJECTIONS UNDER 35 USC 112

In the Office Action, the Examiner has maintained the rejections of claims 64, 68-95, 105-108 and 110 under 35 USC 112 first paragraph. Specifically, the Examiner asserted that the specifications failed to provide an enabling disclosure for utilizing any other embryonic stem cell line other than ESF 116 cell line. The Examiner asserted that the specification clearly teaches that culturing of the mouse ES cells to produce dendritic cells is unpredictable.

Applicants traverse and disagree with the Examiner's assertion. Applicants maintain that one skilled in the art can make any mouse and human dendritic cells from any mouse and human ES cells, based on the method disclosed in the subject application. As evidence,

Applicants are attached hereto as Appendix 1, a Declaration by Paul Fairchild, an expert in stem cells biology.

The Declaration demonstrate that the Examiner is incorrect in the basis for the rejection. The application discloses and teaches one skilled in the art how to make dendritic cells from mouse or human ES cells. The examples provided in the application show that ES cells derived from at least three mouse strains were effective in differentiating into dendritic cells:

> "[i]n support of the latter possibility, initial studies on the CBA/Ca cell line ESF116 were repeated using a second CBA/Ca line generated in-house (ESF99) and one from 129/Sv mice, which is widely used for gene knockout technology and which is commercially available. Interestingly, while ESF99 supported the development of esDC, albeit to a lesser extent than ESF116, D3 failed entirely to do so under the same culture conditions ES cells generated from other strains can easily be tested for their ability to support development of DC by using the protocols described herein. An additional example of a mouse strain from which ES cells have been shown to support development of DC is C57BL/6 (ESF75)". [Page 8 lines 19-31] demonstrating the results

Furthermore, other mouse ES cell lines, behaves identically with respect to the production of dendritic cells. Furthermore, Cheng *et al.* [*Blood* (2003) **102**:3980-3988] have reported the successful use of a commercially available mouse ES cell line derived from 129 mice (R1) for the generation of dendritic cells according to the teachings of the invention.

As demonstrated in the application, since at least three mouse ES cell lines (CBA/Ca, ESF99 and ESF 116) were effective in producing a long-term culture of immature dendritic cells, by culturing the ES cells in the presence of a composition comprising IL-3, one skilled in the art would be enabled to practice the invention without undue experimentation, namely to generate dendritic cells from any mouse ES cell line.

In addition, it is known to those skilled in the art that there is significant conservation of the developmental processes between mouse and human, particularly with respect to

hematopoiesis. Based on the disclosed described methods, material and experiments of mouse ES cell line in the application, one skilled in the art can obtain dendritic cells from human ES cell lines.

It is noted in the Declaration that it has been difficult to obtain human ES cells in both Europe and the United States to conduct such work due to ethical and regulatory restrictions.

As explained in the Declaration ,**deriving dendritic cells from human ES cells** was demonstrated by Zhan *et al.* (2004) [*Lancet* **364**:163-171] who generated a broad range of hematopoietic cell types from human ES cells, including dendritic cells. Zhan *et al.* state that "to generate a broad range of haematopoietic cells, including dendritic cells and other antigen-presenting cells, we adapted a protocol developed previously for mouse ES cells" [p164, column 2, paragraph 3] and cite Fairchild *et al.*, (2000) [*Curr. Biol.* **10**:1515-1518] in this respect, which method corresponds to the method of the subject application. Zhan *et al.* apply the protocol for the production of dendritic cells, using IL-3 as claimed in the subject application. In order to broaden the range of leukocytes obtained, so as to make their results applicable to their stated objective, Zhan *et al.* added a number of other growth factors, namely (i) stem cell factor, (ii) Flt3 ligand and (iii) thrombopoietin, each of which they acknowledge to be "widely used to maintain human postnatal haematopoietic stem cells and to expand committed progenitor cells" [p164; column 2, paragraph 3], in accordance with the literature [Luens *et al.* (1998) *Blood* **91**:1206-1215; Koizumi *et al.* (1998) *Exp. Hematol.* **26**:1140-1147]. The addition of IL-4 to the culture medium was purely to "enhance possible maturation of lymphoid cells and dendritic cells" [p165, column 1, lines 1-2]. Thus, as is shown in the Decalration, Zhan et al. obtain dendritic cells from human ES cells based on the method disclosed in the subject application.

Therefore, contrary to the Examiner's assertion the subject application is enabled without any undue experimentation for obtaining any mouse and human dendritic cells ES cells.

No fee is deemed necessary for filing this Amendment. However, if any fee is required, the undersigned Attorney hereby authorizes the United States Patent and Trademark Office to charge 05-0649.

Respectfully submitted,

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